

The Nonthyroidal Illness Syndrome

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The evaluation of altered thyroid function parameters in systemic illness and stress remains complex because changes occur at all levels of the hypothalamic-pituitary-thyroid axis. The so-called “nonthyroidal illness syndrome,” also known as the low T3 syndrome or euthyroid sick syndrome, is not a true syndrome but rather reflects alterations in thyroid function tests in a variety of clinical situations that commonly include a low serum triiodothyronine (T3), normal to low thyroxine (T4), and a high reverse T3 (rT3). These typical changes may be observed in up to 75% of hospitalized patients [1]. We generally assess measurements of thyroid hormone levels and thyrotropin (TSH) to ascertain the systemic metabolic state of the patient. Despite accurate and precise techniques, these measurements may not be indicative of true thyroid hormone action at the cellular level because of alterations in intracellular thyroid hormone uptake, receptor binding, and hormone binding to their serum transport proteins in systemic illness [2–4]. Thyroid function abnormalities can occur within hours of acute illness, and the magnitude of these alterations correlates with severity of disease with the lowest T3 and T4 values associated with decreased survival. Although it has been concluded that the probability of death is 50% when serum T4 is less than 4 µg/dL and increases to 80% when serum T4 is less than 2 µg/dL, evidence suggests that low T3 is an independent predictor of survival [5–8], as are elevated rT3 and decreased T3/rT3 [9]. This article briefly summarizes thyroid function alterations generally seen in the euthyroid sick syndrome, provides an overview of specific thyroidal adaptations during several clinical conditions and secondary to specific pharmacologic

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agents, and discusses the current controversy in thyroid hormone treatment of nonthyroidal illness.

Alterations of thyroid economy with nonthyroidal illness

Thyroid hormone parameters in nonthyroidal illness have been reviewed in detail elsewhere [10]. We provide a brief summary of the changes typically observed.

Triiodothyronine

Low serum T3 is the most common manifestation of altered thyroid economy in nonthyroidal illness. The enzyme 5'-deiodinase catalyzes the monodeiodination of approximately 35% to 40% of circulating T4 to produce the active hormone T3, thereby accounting for 80% to 90% of T3 in the circulation; the remaining 10% to 20% of T3 is directly secreted by the thyroid. Inhibition of 5'-deiodinase is believed to occur in nonthyroidal illness, resulting in a decrease in T4 to T3 conversion in a variety of tissues and hence low serum T3 concentrations [2].

Thyroxine

Generally, decreases of serum T4 are seen in nonthyroidal illness and can be due to hypothalamic-pituitary suppression, disordered iodine uptake, abnormal peripheral metabolism, or decreased binding to carrier proteins such as thyroid hormone binding globulin (TBG). Measurements of free T4 are commonly within the normal reference range but may be low or slightly increased depending upon the specific underlying disease process [10–12].

Serum reverse triiodothyronine

rT3 is usually elevated in nonthyroidal illness. T4 to rT3 conversion by 5-deiodinase is called the “inactivating pathway.” With impairment of 5'-deiodinase activity reducing metabolism of T4 by the activating pathway, more T4 substrate is available for 5-deiodinase action via the inactivating pathway and hence conversion to rT3. In addition, 5'-deiodinase ordinarily converts rT3 to T2, and reduced activity of 5'-deiodinase slows clearance of rT3, further elevating rT3 levels. In the setting of low serum T3 and T4 in systemic illness, the differential diagnosis would include hypothyroidism. Previously, measurements of rT3 were said to be useful to differentiate nonthyroidal illness (with its high rT3) from hypothyroidism (which should be associated with low rT3), but subsequent studies have shown that rT3 does not accurately distinguish the two states [13].

Thyrotropin

TSH measurements most commonly within the normal reference range in nonthyroidal illness has been the strongest held evidence that these patients are “euthyroid” and is responsible for the continuing popularity of the designation “euthyroid sick syndrome.” Depending upon the etiology of the underlying nonthyroid illness, TSH levels may be low, but only on rare occasions are TSH levels undetectable due to nonthyroidal illness alone. TSH may be transiently elevated even to greater than 20 mU/L during nonthyroidal illness recovery [2].

Altered thyroid economy in specific clinical conditions

Starvation and fasting

The fasting state causes a down-regulation in the hypothalamic-pituitary-thyroid axis and hence decreased thyroid hormone levels [14,15]. It may be difficult to distinguish between the effects on thyroid function of a given systemic illness versus those of the associated absolute or relative starvation because malnutrition is a component of many acute and chronic diseases. The decreased serum T3 in starvation is hypothesized to reflect an attempt by the organism to conserve energy by reducing metabolic expenditure. Investigative endeavors to restore serum T3 to the normal range during starvation have resulted in evidence of increased muscle catabolism [16,17]. Therefore, starvation-associated alterations in thyroid function different from those observed in the fed state may not be abnormal but rather may represent appropriate alterations reflecting maintenance of homeostasis.

In the fasting state, substantial decreases in serum total and free T3 are seen within 24 to 48 hours primarily due to the down-regulation of peripheral 5'-deiodination of T4 to T3. The increase in rT3 during fasting is mainly due to decreased metabolic clearance of rT3 by 5'-deiodinase rather than increased rT3 production from 5-deiodination of T4 to rT3 [10]. On the other hand, total T4 concentration may change little, and free T4 levels most commonly remain unchanged or may show slight increases due to fasting-induced elevations in plasma free fatty acids (known to occur during fasting), which inhibit hormone protein binding [18]. Free T4 returns to normal within 2 weeks of continued fasting [10], although total T4 may exhibit steady decreases corresponding to the fall in thyroid binding globulin seen with prolonged minimal caloric intake [19]. Long-term caloric restriction in humans (range, 3–15 years) with adequate protein intake is associated with a “chronic” low T3 syndrome [20].

Alterations in the regulation of thyroid hormone economy during starvation occur not only peripherally via effects on deiodination and hormone binding; changes also occur centrally. Reduced thyroidal secretion of thyroid hormones is thought to be due in part to suppression of TRH

expression within the hypothalamic paraventricular nucleus leading to decreased stimulation of TSH production [21]. In addition, altered glycosylation of newly synthesized TSH reduces TSH bioactivity and hence decreases thyroid hormone secretion [21]. Not only are TSH and TRH levels decreased with prolonged fasting, but the TSH response to TRH is also blunted [22]. A key factor causing a fall in TRH expression is a rapid decrease in the hormone leptin, which is known to be a major signaling protein during the transition from the fed to the starved state [23]. Leptin is expressed mostly in adipose cells, and a decrease in leptin increases appetite, decreases energy expenditure, and modifies neuroendocrine function to favor survival during starvation [24]. The mechanisms by which leptin modifies TRH expression or TSH secretion are unclear: Leptin may act directly via leptin receptors on TRH neurons or indirectly via the hypothalamic melanocortin pathway [25]. Exogenous r-metHuLeptin administration has been shown to prevent the fasting-induced changes of TSH but has had no effect on the fasting-induced changes in T3 and rT3; this finding suggests that leptin has no direct effect on deiodinase activity [26], but more studies are needed to further elucidate these mechanisms.

Thyroid function is affected not only by caloric content but also by dietary composition. Reduced carbohydrate intake causes decreased T3, increased rT3, and decreased thyroid binding globulin levels [27]. Evidence suggests that in fasting subjects, refeeding with 50 g of carbohydrate (200 kcal) can reverse fasting-induced changes in T3 and rT3 [28], but refeeding with protein and fat cannot normalize T3 levels [29]. Because 5'-deiodinase contains selenium, a relationship between selenium deficiency and low T3 levels during fasting or nutritional deficiency had been surmised; however, several prospective, placebo-controlled trials have concluded that low T3 levels during starvation and other severe illnesses are not directly related to selenium deficiency [30].

Infectious disease

The development of the nonthyroidal illness syndrome during infection and sepsis involves central and peripheral mechanisms, including decreased TSH secretion from the pituitary, reduced thyroidal secretion of T4 and T3, and impaired peripheral T4 to T3 conversion. These changes contribute to low T4, free T4, T3, and TSH and occur early in the course of sepsis. Because increased cytokine release is predominantly observed in sepsis as compared with nonseptic diseases [31], attention has recently been focused on the role of cytokines in the development of nonthyroidal illness syndrome in the setting of sepsis and severe inflammatory states. Evidence suggests that the cytokines interleukin (IL)-1 β , soluble IL-2 receptor, IL-6, tumor necrosis factor- α , and nuclear factor κ B have roles in the direct suppression of TSH in sepsis [31–34]. Nutritional deprivation during sepsis and severe illness also contributes to altered thyroidal economy in these settings [35].

Although earlier reports hypothesized that endogenous glucocorticoids suppressed pituitary function, including TSH secretion in severe illness [36], more recently endogenous glucocorticoids were found to have little if any contribution to the development of nonthyroidal illness syndrome [31]. The degree of thyroid function test alterations directly relates to infection severity [37].

In most patients who have infections due to HIV, thyroid function parameters, including T3, free T4, and TSH, remain normal unless severe disease is present due to low CD4 cell counts [38–40]. One measurement that may be altered is the serum TBG. Increases in TBG have been observed in the HIV population for reasons that remain unclear but seem unrelated to hepatic dysfunction. The mechanism might relate to altered TBG sialylation, which is known to decrease TBG clearance as seen in pregnancy and other states of elevated serum estrogen levels [41]. In one study of patients who had *Pneumocystis carinii* pneumonia and AIDS, low serum T3 values were associated with increased mortality. In addition, serum rT3 levels were low in the outpatient setting and normalized after hospitalization for severe illness. Unlike other causes of nonthyroidal illness syndrome, rT3 levels were not markedly elevated in this group of patients who had AIDS [42]. In one study of HIV-infected patients receiving highly active antiretroviral therapy, 23 out of 182 patients (12.6%) demonstrated lower free T4 and higher TSH levels, which is suggestive of subclinical or mild hypothyroidism [43]. This could be due to immune reconstitution with the unmasking of underlying Hashimoto disease that was previously quiescent.

Cardiac disease

Thyroid hormone is a key modulator of cardiovascular functions, including heart rate, cardiac contractility, cardiac output, and peripheral vascular resistance [44,45]. Alterations in thyroid function tests in cardiac disorders are frequently observed with cardiac ischemia, congestive heart failure, and after coronary artery bypass grafting. Decreased T3, increased rT3, and decreased TSH and T4 have been found in acute myocardial infarction and unstable angina, with the degree of T3 decrease and rT3 increase proportional to the severity of disease. In these groups of patients, thyroid function test changes were not affected by β -blockers or thrombolytics [46]. One prospective study investigating thyroid function in cardiac arrest found total and free T3 to be significantly lower in patients after cardiac arrest induced by acute coronary syndrome as compared with patients who had acute uncomplicated myocardial infarction or healthy control subjects. There were no significant differences between total T4, free T4, and TSH levels among the groups. Much lower values of free and total T3, free and total T4, and TSH were found in those who sustained prolonged cardiac arrest than in those whose duration of cardiac arrest was shorter, and thyroid function tests normalized at 2 months in those who survived [47].

The prevalence of a nonthyroidal illness syndrome in congestive heart failure is approximately 18% according to a recent prospective trial [48] and may be as high as 23% [49]. Patients categorized as New York Heart Association (NYHA) class III-IV are more likely to have thyroid function test abnormalities consistent with nonthyroidal illness syndrome than are patients who have NYHA class I-II heart failure. Deaths in heart failure patients who have nonthyroidal illness syndrome are significantly more frequent than in heart failure patients who have normal thyroid function tests, and heart transplant normalizes thyroid function tests in patients who have heart failure and nonthyroidal illness syndrome [48]. In addition, so-called “subclinical” hypothyroidism (defined as a TSH level above the upper limit of normal but with a normal free T4) is even more prevalent than nonthyroidal illness syndrome in patients who have NYHA class II-III congestive heart failure [49]. Low T3 has been prospectively shown to be an independent predictor of mortality in hospitalized cardiac patients [50].

Renal disease

That impaired renal function can cause perturbations in thyroidal economy is not unexpected given the kidney's role in the metabolism and excretion of thyroid hormone. In the nephrotic syndrome characterized by proteinuria exceeding 3 g daily, hypoalbuminemia, hyperlipidemia, and edema, T3 levels are decreased. This was thought to be due to loss of TBG in the urine along with other proteins [51]; however, TBG levels are normal in many patients who have nephrotic syndrome and a preserved glomerular filtration rate (GFR) but are decreased if the degree of proteinuria is high secondary to a severely reduced GFR [52]. Serum rT3 levels are typically normal to low in nephrotic syndrome [52], in contrast to other forms of nonthyroidal illness syndrome typically characterized by elevated rT3. Glucocorticoids commonly given to treat nephrotic syndrome may complicate the interpretation of thyroid function tests because they may lower TSH secretion and decrease T4 to T3 conversion; in this setting, serum rT3 may be normal to elevated. Free T4 and free T3 are typically normal in nephrotic syndrome, and thyroid hormone supplementation should be reserved for patients who have at least mild TSH elevations as a consequence of large-scale proteinuria and excess thyroid hormone wasting in the urine or with low serum free T4 in the setting of glucocorticoid use.

End-stage renal disease (ESRD) alters the hypothalamic-pituitary-thyroid hormone axis in addition to peripheral thyroid hormone metabolism [53]. ESRD leads to decreased total and free T3 because of reduced T4 to T3 conversion. Enhanced clearance of T3 from plasma does not occur in renal failure and thus cannot account for the low serum T3 [10,54]. Chronic metabolic acidosis in ESRD may contribute to low free T3 levels [55], and low free T3 has been prospectively shown to be an independent predictor of mortality in hemodialysis patients [56]. Another striking difference from other nonrenal

causes of nonthyroidal illness syndrome is the absence of a coexisting increase in the conversion of T4 to rT3 because rT3 levels are most commonly normal in ESRD [57–60]. Although the clearance rate of serum rT3 is impaired in ESRD, the apparent redistribution of rT3 from vascular to extravascular spaces and enhanced intracellular entry of rT3 may account for failure to observe a further increase in serum rT3 levels [37,60]. Total and free T4 are generally slightly decreased or normal, but free T4 may be increased in the setting of heparin used for anticoagulation during hemodialysis because heparin is known to inhibit T4 binding [61]. TSH levels are generally normal in ESRD, but TSH glycosylation is abnormal, which may affect the plasma half-life of TSH [53]. The TSH response to TRH is typically blunted, with a delayed peak and prolonged return to baseline, perhaps due to reduced renal clearance of TSH, TRH, or both [62–64]. Hemodialysis does not tend to normalize the abnormal thyroid function parameters observed in ESRD, but these alterations are largely reversed after renal transplant. Interpretation of thyroid function test in the renal transplant population is complicated by chronic posttransplant glucocorticoid use in many recipients, and persistent attenuation of the response of TSH to TRH may be attributable to steroids, especially if higher doses are used [10,53,54].

Hepatic disease

Normal liver function is important to thyroid metabolism because the liver is the principal site of T4 to T3 conversion via 5'-deiodination, thyroid hormone carrier protein (TBG and albumin) synthesis, T4 uptake, and secondary T4 and T3 release into the circulation. Abnormalities in thyroid function tests vary based on the type and severity of hepatic dysfunction. The abnormalities observed in cirrhosis, acute hepatitis, and chronic liver disease are described below.

The most common thyroid function test abnormalities in cirrhosis are low total T3, low free T3, and elevated rT3. The plasma T3:rT3 ratio is inversely related to the severity of cirrhosis [65,66]. Free T4 may increase and total T4 may decrease secondary to changes in TBG and albumin binding properties and concentrations. Although patients who have cirrhosis may have increased rather than normal TSH levels typically seen in nonthyroidal illness syndrome, they generally remain clinically euthyroid and have normal to delayed TSH and thyroid hormone responses to TRH injection [10,67].

The thyroid function test abnormalities that occur in acute hepatitis differ markedly from those seen with other forms of liver disease and severe illness. Increased TBG is released from the liver as an acute-phase reactant with concomitant elevations in serum total T3 and total T4 levels. Free T4 and TSH are most commonly normal, but minimal elevations in rT3 and reductions in free T3 may be observed [68]. Evidence suggests that the rT3:T3 ratio may have value in assessing the severity of hepatitis and the prognosis of patients who have fulminant hepatitis. For example, the

rT3:T3 ratio quickly normalizes in survivors of fulminant hepatitis but does not improve in nonsurvivors [69].

Although diseases such as chronic autoimmune hepatitis and primary biliary cirrhosis are chronic diseases, their associated thyroid function test abnormalities more closely parallel those of acute hepatitis than those of cirrhosis. Similar to acute hepatitis, serum TBG levels are elevated, with an associated increase in total T4 and T3 concentrations. In contrast to cirrhosis and acute hepatitis, free T4 and free T3 levels are more likely to be low [67,70]. Because these forms of liver dysfunction have an autoimmune etiology, there is a higher incidence of coexisting autoimmune thyroid disease that must be distinguished from nonthyroidal illness syndrome. Up to 34% of patients who have primary biliary cirrhosis have antithyroid microsomal antibodies, and 20% have antithyroglobulin antibodies [71]. Such patients are likely to have Hashimoto thyroiditis and a propensity to develop subclinical or overt hypothyroidism with thyroid function test abnormalities superimposed upon those of the nonthyroidal illness syndrome. The degree of thyroid function abnormalities may not correlate with the severity of liver dysfunction in chronic autoimmune hepatitis and primary biliary cirrhosis in contrast to the stronger correlations in cirrhosis and acute hepatitis [10].

Effects of drugs on thyroid economy

Pharmacologic agents administered to patients who have systemic illness may confound the interpretation of thyroid function tests. A complete review of drug effects on the hypothalamic-pituitary-thyroid axis is beyond the scope of this article and has been reviewed previously [72,73]. The following section highlights the alterations in thyroid function parameters secondary to drugs commonly used in severe systemic illness.

Glucocorticoids

Often given in so-called stress doses in critical illness, glucocorticoids affect the hypothalamic-pituitary-thyroid axis at multiple levels, including the acute suppression of TSH secretion, down-regulation of T4 to T3 conversion by 5'-deiodinase, and decrease of TBG concentration and hormone-binding capacity [10]. Together, these alterations result in low TSH, low T3, low T4, and normal to slightly low free T4; these changes may be seen as soon as 24 to 36 hours after glucocorticoids are initiated [72,74-78].

Dopamine

Dopamine is administered intravenously in the intensive care setting for its high-dose pressor effects and, at some clinical centers, for its low-dose renal perfusion effects. Prolonged use of dopamine (ie, for several days) can result in precipitous TSH suppression and hence low T4, free T4, T3, and

free T3, which may lead to secondary hypothyroidism with worsening prognosis until thyroid hormone replacement is given [10,79].

Amiodarone

Amiodarone, commonly administered for its antiarrhythmic effects, has a high iodine content reported to be 37% [10]. Amiodarone may increase or decrease thyroid hormone secretion and inhibits T4 to T3 conversion by 5'-deiodinase, resulting in decreased T3 and increased rT3 levels [80]. Amiodarone slows T4 metabolism, leading to T4 and free T4 elevations, and may cause short-term TSH increases [80]. Although the T4 effects may persist, T3 and TSH generally normalize after several months on amiodarone [37,81]. Most patients remain euthyroid on amiodarone, but the drug causes hypothyroidism in 5% to 25% of patients (more common in regions with adequate iodine intake) and hyperthyroidism in 2% to 10% of patients (especially in iodine-deficient regions) [45].

Furosemide

At common therapeutic doses, furosemide has little if any effect on thyroid parameters. At higher doses that may be used during hospitalization for aggressive diuresis (ie, > 80 mg intravenously), furosemide causes a transient elevation in free T4 and a decrease in T4 due to the displacement of T4 from TBG. The magnitude of change depends on a number of factors including serum concentrations of albumin, which also bind furosemide [72,82–84].

Salicylates

Salicylates cause a transient increase in free T4 due to inhibition of T3 and T4 binding to TBG in a similar manner to furosemide. This effect is seen in high doses (ie, > 2 g daily), and once a steady-state of the drug is achieved, free T4 normalizes with a 20% to 30% decrease in T4 [72,85–87].

Phenytoin

Phenytoin increases the rate of hepatic metabolism of T4 and T3 and may cause decreases in free T4 and rT3 but with generally normal TSH [2]. Free T4 measurements by equilibrium dialysis suggest that free T4 continues to be normal [72]. The effects of phenytoin on T3 and free T3 are variable, and these parameters may be depressed or remain normal in patients receiving this medication [88,89].

Beta-adrenergic-antagonists

Propranolol may cause minimal inhibition of 5'-deiodinase, thereby decreasing T3 and increasing rT3 [73], but propranolol does not cause increased thyroidal secretion [90].

Iodine

Iodine is a constituent of the intravenous contrast agents routinely used for CT studies and cardiac catheterization procedures. Iodine acutely reduces thyroid hormone secretion and exacerbate hypothyroidism. Conversely, large iodine loads can precipitate thyrotoxicosis in patients who have underlying autonomous thyroid function [2].

Thyroid hormone treatment during nonthyroidal illness

The commonly held notion that patients who have nonthyroidal illness are euthyroid continues to be debated [1,5,91–97]. The metabolic state in these patients has been deemed to be euthyroid based on generally normal TSH and free T4 measurements. Changes in thyroidal economy may play an adaptive role in times of stress, but consideration has also been given to the possibility that patients who have nonthyroidal illness and low thyroid hormone levels may not respond with elevated TSH due to central hypothyroidism from systemic illness. Because hypothyroidism exacerbates the condition of many underlying disease processes, thyroid hormone administration has been considered for treatment in patients who have nonthyroidal illness. Because thyroid hormone is not without adverse effects, including precipitating coronary ischemia, myocardial infarction, arrhythmia, or death at supraphysiologic thyroid hormone levels [98,99], the issue of thyroid hormone treatment continues to be controversial.

Work in models involving organ donors who had suffered brain death where thyroid hormone replacement was given in the organ transplant setting and benefits in cardiac inotropic function were observed [100,101] has led to investigations with thyroid hormone administration in systemic illness. During coronary artery bypass grafting and in the immediate postoperative period, total T3 decreases transiently. Several studies have investigated the use of intravenous T3 replacement during coronary artery bypass grafting, and although this normalizes decreases in total T3, no significant effect on perioperative morbidity and mortality has been found. Furthermore, although perioperative intravenous T3 administration resulted in lower systemic vascular resistance and improved cardiac output, there was no change in frequency of arrhythmia, hemodynamic stability, duration of stay in the intensive care unit, or inotropic drug requirements [102,103].

Evidence suggests that T3 administration may exert negative effects on protein and fat metabolism [16,104,105], adversely affect catecholamine levels found to increase as T3 and T4 levels decrease in critical illness [106], and cause deleterious cardiac effects. Thyroid hormone replacement during fasting [103], in patients who have ESRD who are on hemodialysis [107], and in burn victims [108] has shown no beneficial effects. In a recent study [109] involving patients who died in the intensive care unit, those who received a combination of T4 and T3 replacement therapy had higher serum

T3 levels and higher levels of T3 in liver and skeletal muscle, with a twofold greater increase in liver T3 than in serum T3. Patients who did not receive thyroid hormone replacement had decreased levels of T4 and T3 in the liver and skeletal muscle. Another study found that TRH infusion normalized peripheral thyroid hormone levels within 1 day in critically ill patients [110]; these investigators hypothesize that this may be a safer alternative to thyroid hormone administration with greater likelihood of avoiding supraphysiologic thyroid hormone levels.

If the clinician determines a trial of thyroid hormone replacement is warranted in a patient who has deteriorating clinical status and thyroid function test results suggestive of hypothyroidism, intravenous T3 administration is preferred over T4 due to reduced 5'-deiodinase activity and hence decreased conversion of T4 to metabolically active T3 in the sick patient. This was confirmed in one study in the intensive care unit that administered intravenous T4 sufficient to normalize T4 and free T4 and found that rT3 increased, whereas T3 did not; these investigators observed no survival benefit between those who did and did not receive thyroxine [111]. The answer to the question of whether or not thyroid hormone administration in nonthyroidal illness has a positive influence on outcome or prognosis in systemic illness is likely to remain unanswered until studies conclusively indicate morbidity and mortality benefits.

Summary

The evaluation of altered thyroid function parameters in systemic illness and stress remains complex because changes occur at all levels of the hypothalamic-pituitary-thyroid axis. Nonthyroidal illness syndrome is generally characterized by low serum T3, normal free T4 and TSH, and elevated rT3 values. Unique changes in thyroid function parameters are observed in various clinical states, including starvation and fasting, cardiac disease, renal disease, hepatic disease, and infection. Many pharmacologic agents cause changes in thyroidal economy that can complicate the interpretation of thyroid function parameters in systemic illness. Although alterations in thyroid parameters may represent adaptive changes to conserve energy expenditure by reducing metabolic activity, some argue that systemic illness may induce a central hypothyroidism. The issue of thyroid hormone replacement remains controversial in the nonthyroidal illness syndrome.

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